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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 487/04, 487/08, 471/08
A61K 31/40, 31/435, 31/55
A61K 31/53, 31/505

A1

(11) International Publication Number: WO 92/15590

(43) International Publication Date: 17 September 1992 (17.09.92)

(21) International Application Number: PCT/US92/01525

(22) International Filing Date: 4 March 1992 (04.03.92)

(30) Priority data:
666,151 7 March 1991 (07.03.91) US

(60) Parent Application or Grant
(63) Related by Continuation
US 666,151 (CIP)
Filed on 7 March 1991 (07.03.91)

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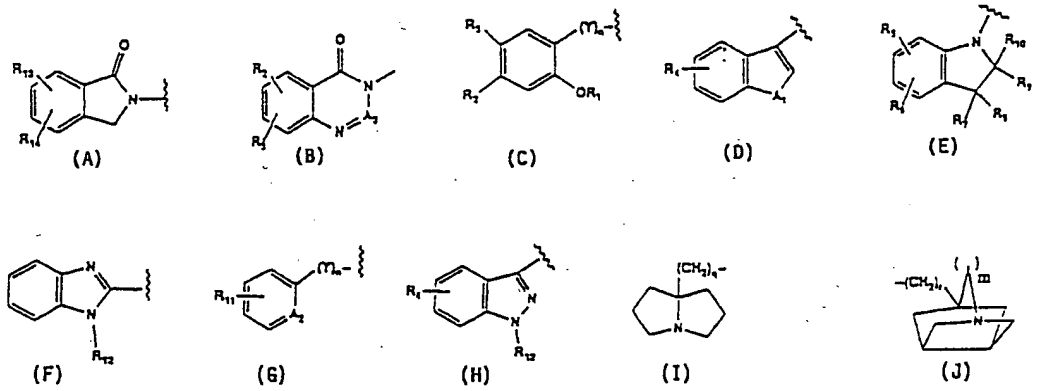
(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NEW MESO-AZACYCLIC AROMATIC ACID AMIDES AND ESTERS AS NOVEL SEROTONERGIC AGENTS



(57) Abstract

Meso-azacyclic aromatic acid amides and esters of formula Ar-(CO-X)p-Z wherein Ar represents a radical of formulae (A, B) and when p is 1, Ar represents a radical of formulae (C, D, E, F, G, H) and Z represents a radical of formulae (I, J) are useful in the treatment of the central nervous system and gastrointestinal motility disorders such as gastroesophageal reflux, non-ulcer dyspepsia, delayed gastric emptying, ileus, irritable bowel syndrome, and the like. Additionally, they find utility as antagonists of serotonin 5-HT_3 receptors, and are useful for the treatment of humans and animals wherein antagonism of 5-HT_3 receptors is beneficial. Therapy is indicated for the treatment of anxiety, psychoses, depression (especially depression accompanied by anxiety), cognitive disorders, substance abuse dependence and/or withdrawal, irritable bowel syndrome, emesis caused by chemotherapeutic agents, and visceral pain. Additionally, they may find utility as enhancers of nasal absorption of bioactive compounds.

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New Meso-Azacyclic Aromatic Acid Amides and Esters as Novel Serotonergic Agents.

BACKGROUND OF THE INVENTION

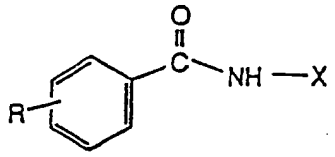
The invention herein is directed to compounds and a method of treating gastrointestinal motility disorders of a mammal by administering to the mammal in need thereof a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof. The method can be practiced to treat gastrointestinal motility disorders such as gastroesophageal reflux, diseases characterized by delayed gastric emptying, ileus, irritable bowel syndrome, and the like. The compounds of the invention are serotonergic 5-HT_3 antagonists and as such are useful for the treatment of conditions, for example, such as anxiety, psychoses and depression.

There are classes of compounds known for the treatment of such disorders. For example, azatetracycle compounds are disclosed in co-pending U.S. patent application serial no. 07/515,391 filed April 27, 1990, and N-Azabicyclo [3.3.0] octane amides of aromatic acids are disclosed in co-pending application serial no. 07/406,205 filed September 11, 1989.

Aza-adamantyl compounds are disclosed in U.S. Patent 4,816,453 and are mentioned generically in U.K. Patent 2,152,049A and European application 0189002A2.

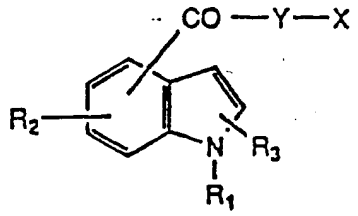
Azabicyclic nonanes are disclosed in European Patent application 0094742A2. Additional azabicyclic compounds are disclosed in U.S. Patents 4,797,387 and 4,797,406.

Benzamides have been known as 5-HT_3 antagonists and as compounds possessing gastrointestinal motility-enhancing properties. Benzamides of the following formula:



compounds wherein X can be an azabicycloalkane moiety and which exhibit gastrointestinal motility enhancing and/or 5-HT_3 antagonist properties are disclosed in EP 0094742A2 and in U.S. patent 4,797,406. In addition, UK Patent 2,152,049 discloses that certain benzamide derivatives exhibit serotonin M antagonistic activity.

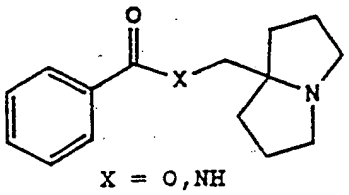
Indoleamides of the following formula have also been described as possessing gastrointestinal motility-enhancing and/or 5-HT_3 antagonist properties:



Compounds wherein X contains an aminergic side chain or an azabicycloalkane moiety are described in U.S. Patent 4,797,406.

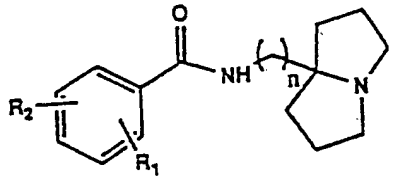
European patent publication number 0,230,718 discloses certain substituted benzamide derivatives, substituted with piperidinyl analogues as having gastrointestinal motility-enhancing and/or antiemetic activity and/or 5-HT receptor antagonist activity.

J. Heterocyclic Chemistry (1987) 24: 47 describes the preparation of the following compound: No substitution is shown in the phenyl ring and no utility is described.



X = O,NH

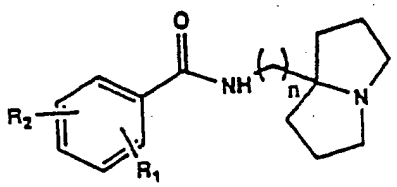
J. Pharmaceutical Sciences (1987) 76: 416 describes compounds of generic scope. Utility as anti-arrhythmic agents is described.



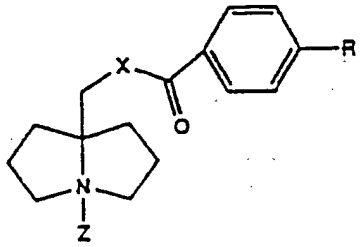
n = 1 or 2

R_1 = H, 2-Me, 4-NH_2, 4-OMe, 4-$NHCO_2Et$, 2-OEt, 4-OEt, 3- or 4-NMe_2, 3- or 4-NO_2; R_2 = H or 6-Me.

JP Patent 58083694 A2 and JP 0027355B describe anti-arrhythmic agents of the following formula wherein n = 1 or 2; R_1 or R_2 are both Me or R_1 is H while R_2 is nitro, di-lower alkylamino, lower alkoxycarbonylamino, or ethoxy.



EP Patent 39,903 and US 4,617,401 describe compounds of the following formula wherein R is H, OMe, OH, or NH_2; X is NH or O; and Z is a lone electron pair or optionally substituted alkyl group. The compounds are described as spasmolytic, antiarrhythmic, and neuromuscular-blocking agents.



SUMMARY OF THE INVENTION

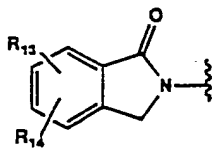
The compounds of the present invention are useful in the treatment of gastrointestinal motility disorders such as gastroesophageal reflux, non-ulcer dyspepsia, delayed gastric emptying, ileus, irritable bowel syndrome, and the like. Additionally, the compounds of the present invention find utility as antagonists of serotonin 5-HT_3 receptors. As such they are useful for the treatment of humans and animals wherein antagonism of 5-HT_3 receptors is beneficial. Therapy is indicated for, but not limited to, the treatment of anxiety, psychoses, depression (especially depression accompanied by anxiety), cognitive disorders, substance abuse dependence and/or withdrawal, irritable bowel syndrome, emesis caused by chemotherapeutic agents, and visceral pain. Additionally, the compounds of the present invention may find utility as enhancers of nasal absorption of bioactive compounds.

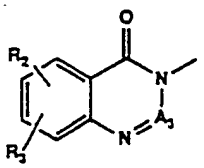
DETAILED DESCRIPTION OF THE INVENTION

The invention herein is directed to compounds of formula I:

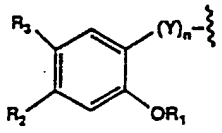
$$Ar-(CO-X)_p-Z \qquad I$$

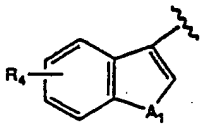
the stereoisomers and pharmaceutically acceptable salts thereof wherein p is 0 or 1 and when p is 0, Ar represents a radical of the formula:

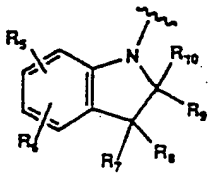


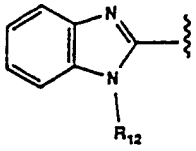


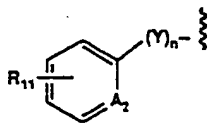
and when p is 1, Ar represents a radical of the formula:

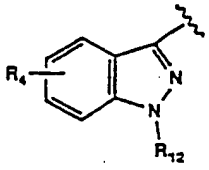










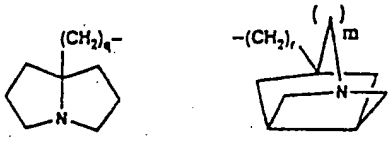


Wherein Y is NH; R_1 is C_{1-6} alkoxy; R_2 and R_3 are independently H, halogen, CF_3, hydroxyl, C_{1-2} alkoxy, C_{2-7} acyl, amino, amino substituted by one or two C_{1-6} alkyl groups, C_{2-7} acylamino, aminocarbonyl, or aminosulfone optionally substituted by one or two C_{1-6} alkyl groups, C_{1-6} alkylsulfone, or nitro; R_4 is H, halo, or C_{1-6} alkoxy; R_5 and R_6 are the same or different and can be H, halo, CF_3, C_{1-6}alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulfonylamino, N-(C_{1-6} alkylsulfonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulfinyl, hydroxy, nitro, or amino, aminocarbonyl, aminosulfonyl, aminosulfonylamino, or N-(aminosulfonyl)-C_{1-4} alkylamino optionally N'-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, or phenyl C_{1-4} alkyl groups or optionally N'-disubstituted by C_{4-5} polymethylene; R_7 and R_{10} can be the same or different and can be H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-4} alkyl or together are C_{2-4} polymethylene; R_8 and R_9 can be the same or different and can be H, C_{1-4} alkyl or taken together are a covalent bond; R_{11} is H or halogen; R_{12} and R_{12}' are the same or different and can be H, C_{1-6} alkyl, or phenyl C_{1-4} alkyl; R_{13} and R_{14} can be the same or different and can be H, halo, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, or amino, aminocarbonyl or aminosulfonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups, or by C_{4-5} polymethylene or biphenyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6}

alkoxy, C_{1-6} alkylthio, hydroxy, or nitro, or when R_{13} and R_{14} are taken together are methylenedioxy or ethylenedioxy; A_1 is O, S, $N(R_{12})$, or CH_2; A_2 is $C\text{-}OR_{12}$, $N^+\text{--}O^-$, CO_2R_{12}, $CONR_{12}(R_{12}')$, SR_{12}, or $SO_2NR_{12}(R_{12}')$; A_3 is N or CH;

X is NH or O; and

Z represents a radical of the formula:



Z_1 Z_2

Wherein m is 1 or 2, n is 0 or 1, p is 1 or 2, q is 1 or 2, and r is 0 or 1.

The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, methyl-butyl, dimethylbutyl and neopentyl.

Included within the family of compounds of the described are the tautomeric forms of the described compounds, isomeric forms including diastereoisomers and individual enantiomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Since the compounds contain basic nitrogen atoms, such salts are typically acid addition salts. The phrase "pharmaceutically-acceptable salts" is intended to embrace alkyl quaternary ammonium salts and n-oxides. The nature of the salt is not critical, provided that it is pharmaceutically acceptable, and acids which may be employed to form such salts are, of course, well known to those skilled in this art. Examples of acids which may be employed to form pharmaceutically acceptable acid addition

salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid, and such organic acids as maleic acid, succinic acid and citric acid. Other pharmaceutically acceptable salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium and magnesium, or with organic bases, such as dicyclohexylamine. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid or base with the corresponding compound of the invention.

The compounds that are the subject of the invention herein can be prepared according to the following reaction schemes.

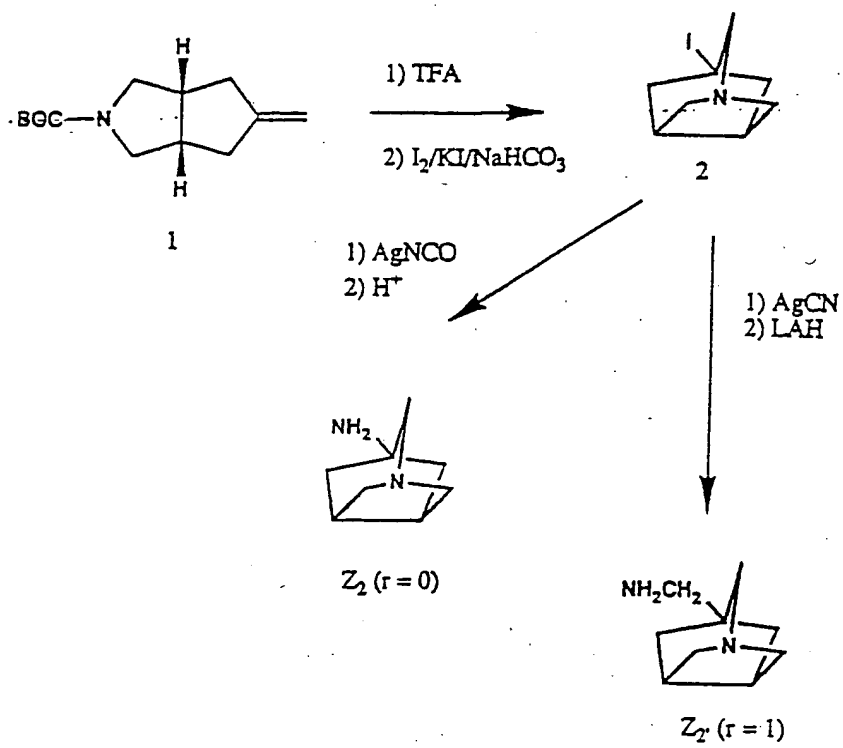
Z_1 is known and is prepared as described by Miyano and coworkers [J. Heterocyclic Chemistry (1987) 24, 47 for q = 1; J. Pharmaceutical Sciences (1987), 76, 416 & references sited therein]. Z_2 is prepared according to schemes 1, 2, and 3.

Scheme 1 describes the preparation of amino-azacycles Z_2. The BOC-amine 1 (U.S. Patent Application serial no. 07/515,391) is deprotected with trifluoroacetic acid and the resulting amine is cyclized intramolecularly with the exocyclic olefin by treatment with iodine and potassium iodide in the presence of sodium bicarbonate to yield the bridgehead iodide 2. Treatment of 2 with silver isocyanate affords the bridgehead isocyanate which may be hydrolyzed to give the requisite amine Z_2 wherein r = 0. Alternatively treatment of 2 with silver cyanide affords the bridgehead nitrile which may be reduced to give the desired aminomethyl-azacycle Z_2 wherein r = 1.

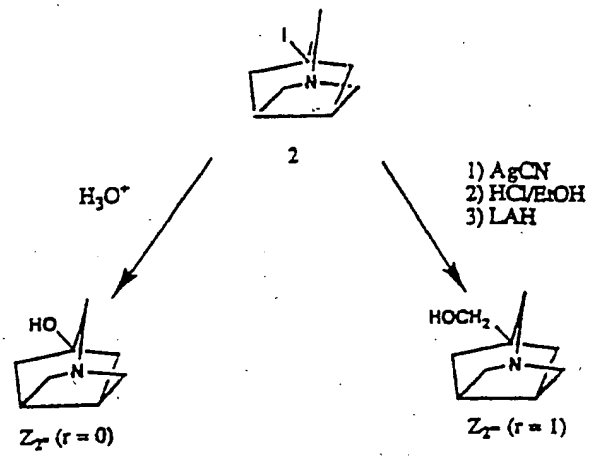
Scheme 2 illustrates the preparation of Z_2 hydroxy azacycles. Hydrolysis of bridgehead iodide 2 affords the desired hydroxy azacycle $Z_{2..}$ wherein r = 0. Alternatively treatment of 2 with silver cyanade followed by hydrolysis and reduction gives the desired hydroxymethyl azacycle $Z_{2...}$ wherein r = 1.

Scheme 3 illustrates the preparation of ethano-bridged azatricycles (Z_2....., wherein m = 2). The azabicycloketone 3 is converted first to its O-benzyloxime. Removal of the N-BOC protecting group, followed by acylation with chloroacetic anhydride & iodide exchange, affords the intermediate 4. Cyclization under reductive radical-cyclization conditions (Bu_3SnH, AIBN) affords the ethano-bridged lactam 5. Reduction with lithium aluminum hydride affords the desired ethano-bridged azatricycle Z_2....

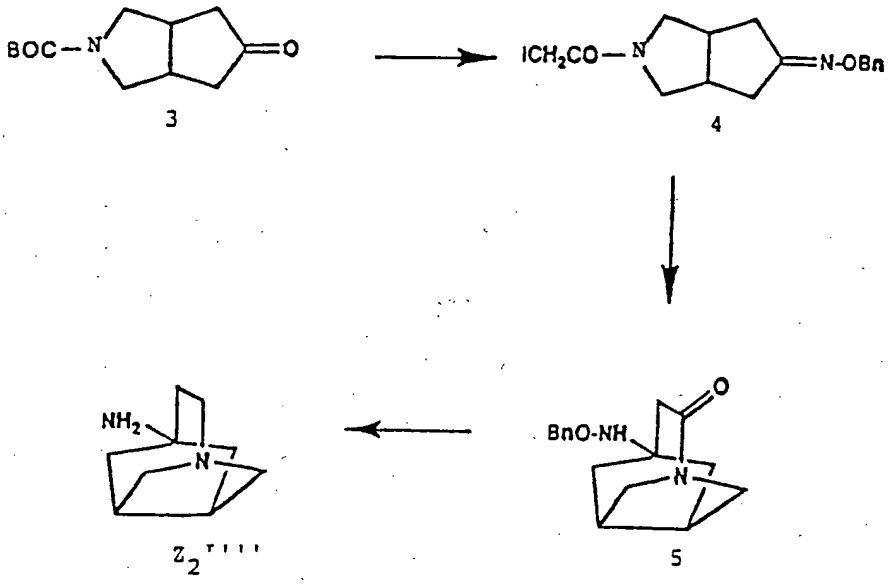
SCHEME 1: PREPARATION OF Z_2 AMINO-AZACYCLES



SCHEME 2: PREPARATION OF Z_2 HYDROXY AZACYCLES



SCHEME 3: PREPARATION OF ETHANO-BRIDGED MESO-AZATRICYCLE

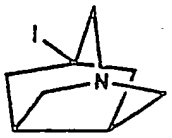


These examples, as well as all examples herein, are given by way of illustration only and are not to be construed as limiting the invention, either in spirit or scope, as many modifications, both in materials and methods, will be apparent from this disclosure to those skilled in the art. In these examples, temperatures are given in degrees Celsius (°C) and quantities of materials in grams and milliliters unless otherwise noted.

EXPERIMENTALS

EXAMPLE A

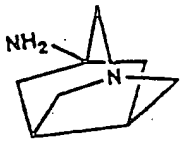
Preparation of hexahydro-5-iodo-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrole



Cis-N-t-butoxycarbonylhexahydro-5-methylenecyclopenta[c]pyrrole [See co-pending Application Serial No. 07/515,391 filed April 27, 1990] is treated with trifluoroacetic acid to afford an intermediate trifluoroacetate ammonium salt, which is then treated with base and I_2 to afford the title compound.

EXAMPLE B

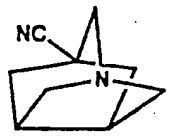
Preparation of tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-5(3H)-amine



The iodo compound prepared in example A is treated with silver isocyanate to afford the intermediate N-formamide. This formamide is hydrolyzed to give the title compound.

EXAMPLE C

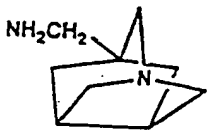
Preparation of tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrole-5(3H)-carbonitrile



The iodo compound prepared in example A is treated with silver cyanide in dimethylformamide to afford the title compound.

EXAMPLE D

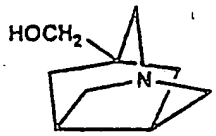
Preparation of tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrole-5(3H)-methanamine



The nitrile compound prepared in example C is reduced with lithium aluminum hydride in etheral solvent to afford the title compound.

EXAMPLE E

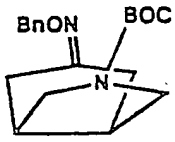
Preparation of tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrole-5(3H)-methanol



The nitrile compound prepared in example C is converted to the intermediate ethyl ester by treatment with aqueous ethanolic HCl. The ethyl ester is then treated with lithium aluminum hydride in etheral solvent to afford the title compound.

EXAMPLE F

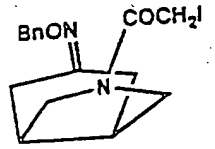
Preparation of 1,1-dimethylethyl hexahydro-5-[(phenylmethoxy)imino]cyclopenta[c]pyrrole-2(1H)-carboxylate



Cis-N-Butoxycarbonylhexahydro-5-oxo-cyclopenta[c]pyrrole is reacted with O-benzylhydroxylamine hydrochloride and sodium acetate in methanol to afford the title compound.

EXAMPLE G

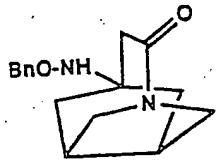
Preparation of octahydro-2-(iodoacetyl)-5-[(phenylmethoxy)imino]cyclopenta[c]pyrrole



The title compound of example F is treated with trifluoroacetic acid in methylene chloride at room temperature. The volatiles are removed under reduced pressure to afford a residue which is treated with chloroacetic anhydride and triethylamine. The chloroacetylated material is then reacted with NaI in acetone to give the title compound.

EXAMPLE H

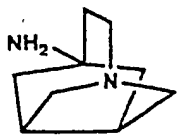
Preparation of hexahydro-5-[(phenylmethoxy)amino]-2,5β-ethano-1H-3aα,6aα-cyclopenta[c]pyrrol-7-one



The title compound of example G is treated with tri-n-butylstannane in benzene at reflux containing a catalytic amount of AIBN. Upon workup the title compound is isolated.

EXAMPLE J

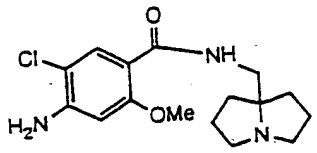
Preparation of tetrahydro-2,5β-ethano-1H-3aα,6aα-cyclopenta[c]pyrrol-5(3H)-amine



The title compound of example H is reacted with lithium aluminum hydride in tetrahydrofuran to afford after workup the title compound.

EXAMPLE 1

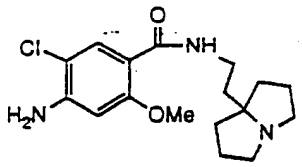
Preparation of 4-amino-5-chloro-2-methoxy-N-(tetrahydro-1H-pyrrolizin-7a(5H)-ylmethyl)benzamide



4-Amino-5-chloro-2-methoxybenzoic acid (134 mg, 0.00095 moles) and 1,1'-carbonyldi-imidazole (151 mg, 0.00095 moles) were suspended in the DMF (2.5 ml) and the mixture was stirred until solution occurred (three hours). At this time, tetrahydro-1H-pyrrolizin-7a(5H)-methylamine [amine J. Het Chem 24, 47, 1987] (134 mg; 0.00095 moles) was added and the mixture was stirred for 2 hours. Tlc 30% MeOH/$CHCl_3$/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was purified by prep tlc chromatography, eluting with 15% MeOH/$CHCl_3$/1/10% NH_4OH to yield 73 mg (24%) of the product. The residue was converted to the HCl salt with MeOH/HCl.

Elements	Calc	Found	
Carbon	53.63	53.57	$C_{16}H_{22}ClN_3O_2$ * 0.7 HCl * 0.5 H2O
Hydrogen	6.67	6.66	
Nitrogen	11.73	11.54	MW 358.35
Chlorine	16.82	16.51	

Example 1A
4-Amino-5-chloro-2-methoxy-N-(tetrahydro-1H-pyrrolizin-7a(5H)-ylethyl)benzamide



Procedure

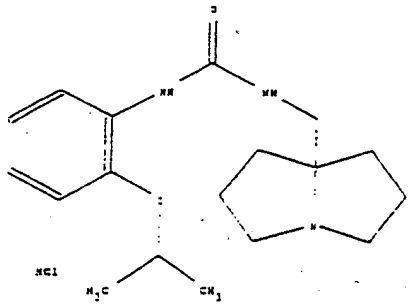
4-Amino-5-chloro-2-methoxybenzoic acid (1.0 g, 0.005 moles) and 1,1'-carbonyldi-imidazole (892 mg, 0.00055 moles) were suspended in the DMF (10 ml) and the mixture was stirred until solution occurred (three hours). At this time, tetrahydro-1H-pyrrolizin-7a(5H)-ethylamine [amine Heterocycles 16, 755, 1981](771 mg; 0.005 moles) was added and the mixture was stirred for 1 hour. Tlc 30% MeOH/$CHCl_3$/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue which was partitioned between Et_2O/H_2O. The product crystallized. The solid was filtered and dissolved in $CHCl_3$, washed with dilute K_2CO_3, dried over $MgSO_4$ and concentrated to a solid. The solid was triturated with Et_2O and converted to the HCl salt with MeOH/HCl to yield 1.27g (69%) of the product.

Elements

Carbon	49.71	49.39	$C_{17}H_{24}ClN_3O_2$ * 2 HCl
Hydrogen	6.38	6.46	
Nitrogen	10.23	10.18	MW 410.77
Chlorine	25.89	25.71	

Example 1B

N'-(tetrahydro-1H-pyrrolizin-7a(5H)-ylmethyl)-2-(2-propyloxy)phenylurea



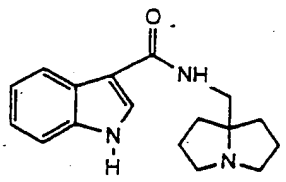
2-isopropoxy-aniline (123 mg, .813 mmole) was dissolved in $CHCl_3$ (1 ml), added triethyl amine (.113 ml, .813 mmole). Cooled soln. to 0°C, added a solution of 20%. phosgene in toluene (.458 ml, .927 mmole) and stirred for 1.5 hours. To this solution was added tetrahydro-1H-pyrrolizin-7a(5H)-methylamine (114 mgs, .813 mmole) in $CHCl_3$ and stirred for 18 hours. Solvent removed via rotary evaporator to give crude product as a solid. Solid was chromatographed on silica gel eluting with 5% $CH_3OH(NH_3\uparrow)/CHCl_3$ to give 220 mg (85%) of title compound as free base.

Calculated for $C_{18}H_{27}N_3O_2$:	Found
C, 67.89	67.96
H, 8.86	8.61
N, 13.19	12.96

Calculated MS for $C_{18}H_{23}N_3O_2$ = 318.44
Found M = 318.215

EXAMPLE 2

Preparation of N-(tetrahydro-1H-pyrrolizin-7a(5H)-ylmethyl)-1H-indole-3-carboxamide



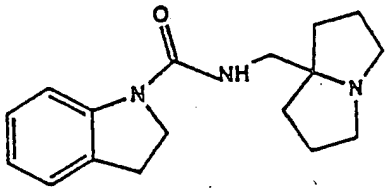
Following the procedure of example 1, 7a-Aminomethylhexahydro-1H-pyrrolizine is reacted with indole-3-carboxylic acid to afford the title compound.

Indole-3-carboxylic acid (161 mg, 0.001 moles) and 1,1-carbonyldiimidazole (162 mg, 0.001 moles) were suspended in the DMF (2.5 ml) and the mixture was stirred until solution occurred (three hours). At this time, tetrahydro-1H-pyrrolizin-7a(5H)-methylamine [amine J. Het Chem 24, 47, 1987] (140 mg; 0.001 moles) and triethylamine (560 µl; 0.004 mole) were added and the mixture was stirred for 1 hour. Tlc 30% EtOH/$CHCl_3$/1/10% NH_4OH indicated that the reaction was complete. Concentration afforded a residue that was partitioned between Et_2O/H_2O. The product crystallized. The solid was filtered and dissolved in $CHCl_3$, washed with dilute NaOH, dried over $MgSO_4$ and concentrated to a solid. The solid was triturated with Et_2O and converted to the HCl salt with MeOH/HCl to yield 174 mg (62%) of the product.

Elements	Calc	Found	
Carbon	62.98	62.68	$C_{17}H_{21}N_3O$ * 0.75 HCl * 0.75 H_2O
Hydrogen	7.23	6.68	
Nitrogen	12.96	12.96	MW 324.23
Chlorine	8.20	8.31	

EXAMPLE 3

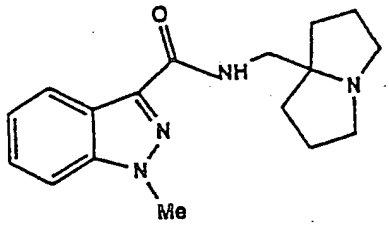
Preparation of 2,3-dihydro-N-(tetrahydro-1H-pyrrolizin-7a(5H)-ylmethyl)-1H-indole-1-carboxamide



7a-Aminomethylhexahydro-1H-pyrrolizine is reacted with indoline-N-trichloromethylcarbamate [J. Medicinal Chemistry (1990) 33: 1929] in toluene at reflux to afford the title compound after extractive workup and column chromatography.

EXAMPLE 4

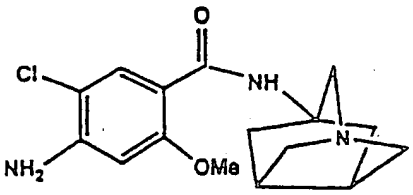
Preparation of 1-methyl-N-(tetrahydro-1H-pyrrolizin-7a(5H)-ylmethyl)-1H-indazole-3-carboxamide



Following the procedure of example 1, 7a-Aminomethylhexahydro-1H-pyrrolizine is reacted with N-methylindazole-3-carboxylic acid [J. Medicinal Chemistry (1987) 30: 1535] to afford the title compound.

EXAMPLE 5

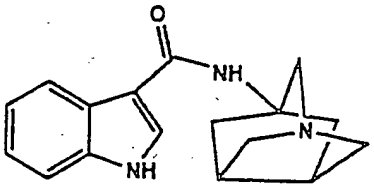
Preparation of 4-amino-5-chloro-2-methoxy-N-(tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-5(3H)-yl)benzamide



N-hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-5α-amine is reacted with 2-methoxy-4-amino-5-chlorobenzoic acid and carbonyldiimidazole in dimethylformamide to afford the title compound.

EXAMPLE 6

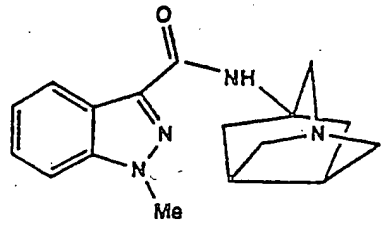
Preparation of N-(tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-5(3H)-yl)-1H-indole-3-carboxamide



N-hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-5α-amine is reacted with indole-3-carboxylic acid according to the procedure of example 5 to afford the title compound.

EXAMPLE 7

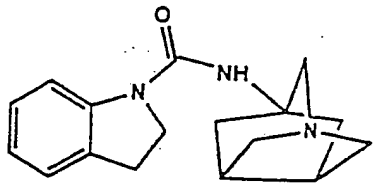
Preparation of 1-methyl-N-(tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-5(3H)-yl)-1H-indazole-3-carboxamide



N-hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-5α-amine is reacted with N-methylindazole-3-carboxylic acid according to the procedure of example 5 to afford the title compound.

EXAMPLE 8

Preparation of 2,3-dihydro-N-(tetrahydro-2,5β-methano-1H-3aα,6aα-cyclopenta[c]pyrrol-5(3H-yl)-1H-indole-3-carboxamide



N-hexahydro-1H-2,5β-methano-3aα,6aα-cyclopenta[c]pyrrol-5α-amine is reacted with indoline-N-trichloromethylcarbamate according to the procedure of example 3 to afford the title compound.

The compounds herein exhibit 5-HT3 antagonism. 5-HT3 antagonism can be determined by the radioligand receptor binding assay as described herein and in the *in vivo* Bezold-Jarisch reflex procedure.

Serotonin (5-HT_3)

Procedure:

GR65630 binds to the 5-HT_3 receptor. Brain cortices are obtained from male rats and a membrane fraction prepared by standard techniques. 0.04 mg of membrane prep is incubated with 0.2 nM [^{3}H]-GR656630 for 60 minutes at 22°C. Non-specific binding is estimated in the presence of 1 uM ICS 205-930. Membranes are filtered and washed 3 times and the filters are counted to determine [3H]-GR65630 specifically bound.*

Results:

Kd = 2.46 nM

Bmax = 154 fmol/mg protein

% Specific Binding: 70

Effect of Reference Compounds on [H]-GR65630 Bound (0.2 nM)			
Compound	IC_{50}	Ki	Hill Coefficient
Quipazine	0.5 nM	0.18 nM	0.86
ICS 205-930	2.2 nM	0.51 nM	1.0
5-HT	122 nM	0.39 uM	1.0
RU24969	320 nM	1.85 uM	1.0
Zacopride	0.55 nM	0.18 nM	0.86

*Literature Reference:

Kilpatrick GJ, Jones BJ and Tyers MB. Identification and distribution of 5-HT_3 receptors in rat brain using radioligand binding. Nature, 330 : 746-748, 1987.

Bezold-Jarisch Reflex

The test sample is administered i.p. (mg/kg) to a group of 3 mice. Thirty minutes later, a 5-HT (0.25 mg/kg i.v.)-induced bradycardia is recorded in pentobarbital anesthetized animals. A greater than 50 percent (>50) reduction in the bradycardic response relative to vehicle-treated control mice is considered significant.

REFERENCE AGENTS:	Minimum Effective Dose (MED) mg/kg
BRL-43694	0.05
cisapride	5
cyproheptadine	5
domperidone	>10
GR-38032	0.5
ketanserin	>10
mecamylamine	2.5
methysergide	>10
metoclopramide	5
scopolamine	2.5

This method has been described by Saxena, P. R. and Lawang, A., Arch. Int. Pharmacodyn., 277:235-252, 1985.

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more of the described compounds in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body

weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

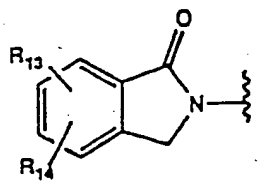
Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

What is Claimed is:

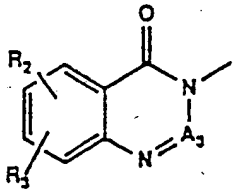
1. A compound of the formula

Ar-(CO-X)p-Z

the stereoisomers and pharmaceutically acceptable salts thereof, wherein p is 0 or 1 and when p is 0, Ar represents a radical of the formula

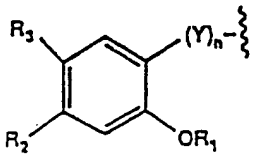


A

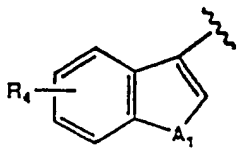


B

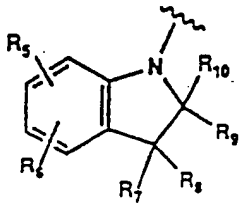
and when p is 1, Ar represents a radical of the formula



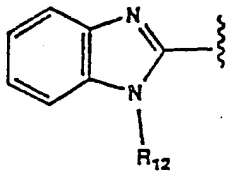
C



D



E



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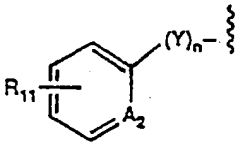
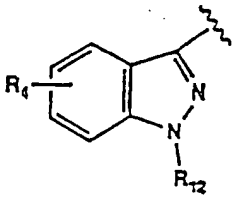


G



H

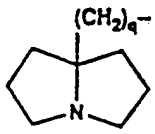
Wherein Y is NH, R_1 is C_{1-6} alkoxy, R_2 and R_3 are independently H, halogen, CF_3, hydroxyl, C_{1-2} alkoxy, C_{2-7} acyl, amino, amino substituted by one or two C_{1-6} alkyl groups, C_{2-7} acylamino, aminocarbonyl, or aminosulfone optionally substituted by one or two C_{1-6} alkyl groups, C_{1-6} alkylsulfone, or nitro, R_4 is H, halogen, or C_{1-6} alkoxy; R_5 and R_6 are the same or different and can be H, halogen, CF_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-7} acyl, C_{1-7} acylamino, C_{1-6} alkylsulfonylamino, N-(C_{1-6} alkylsulfonyl)-N-C_{1-4} alkylamino, C_{1-6} alkylsulfinyl, hydroxy, nitro, or amino, aminocarbonyl, aminosulfonyl, aminosulfonylamino, or N-(aminosulfonyl)-C_{1-4} alkylamino optionally N'-substituted by one or two groups selected from C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl or phenyl C_{1-4} alkyl groups optionally N'-disubstituted by C_{4-5} polymethylene, R_7 and R_{10} can be the same or different and can be H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-4} alkyl or together are C_{2-4} polymethylene, R_8 and R_9 can be the same or different and can be H, C_{1-4} alkyl or taken together are a covalent bond, R_{11} is H or halogen, R_{12} and R_{12}' are the same or different and can be H, C_{1-6} alkyl, or aralkyl, R_{13} and R_{14} can be the same or different and can be H, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, or amino,

aminocarbonyl or aminosulfonyl optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups, or by C_{4-5} polymethylene or biphenyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy, or nitro, or when R_{13} and R_{14} are taken together are methylenedioxy or ethylenedioxy;

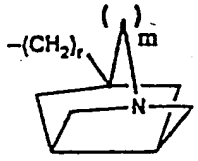
A1 is O, S, $N(R_{12})$, or CH_2; A_2 is $C\text{-}OR_{12}$, $N^+\text{--}O^-$, CO_2R_{12}, $CONR_{12}(R_{12}')$, SR_{12}, or $SO_2NR_{12}(R_{12}')$; A_3 is N or CH;

X is NH or O; and

Z represents a radical of the formula



Z_1



Z_2

Wherein m is 1 or 2, n is 0 or 1, p is 1 or 2, q is 1 or 2 and r is 0 or 1.

2. A compound according to claim 1 wherein p is 0.

3. A compound according to claim 2 wherein Ar is group A.

4. A compound according to claim 3 wherein Z is Z_1.

5. A compound according to claim 3 wherein Z is Z_2

6. A compound according to claim 1 wherein p is 1.

7. A compound according to claim 6 wherein Ar is group C.

8. A compound according to claim 7 wherein Z is Z_1.

9. A compound according to claim 7 wherein Z is Z_2.

10. A compound according to claim 7 wherein Ar is 2-chloro-5-methoxyanilin-4-yl.

11. A compound according to claim 10 wherein Z is Z_1.

12. A compound according to claim 10 wherein Z is Z_2.

13. A compound according to claim 6 wherein Ar is group D.

14. A compound according to claim 13 wherein Z is Z_1.

15. A compound according to claim 13 wherein Z is Z_2.

16. A compound according to claim 13 wherein Ar is indol-3-yl.

17. A compound according to claim 16 wherein Z is Z_1.

18. A compound according to claim 16 wherein Z is Z_2.

19. A compound according to claim 6 wherein Ar is group E.

20. A compound according to claim 19 wherein Z is Z_1.

21. A compound according to claim 19 wherein Z is Z_2.

22. A compound according to claim 6 wherein Ar is group H.

23. A compound according to claim 22 wherein Z is Z_1.

24. A compound according to claim 22 wherein Z is Z_2.

25. A pharmaceutical composition for the treatment of anxiety, psychoses, depression, gastrointestinal motility disturbancies or conditions response to 5-HT_3 antagonist effect comprising a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier or diluent.

26. A pharmaceutical composition according to Claim 25 wherein the compound is selected from the group wherein Ar is group A, C, D, E or H; Z is Z_1 or Z_2; and p is 0 or 1.

27. A pharmaceutical composition according to Claim 26 wherein Ar is group C and p is 1.

28. A pharmaceutical composition according to Claim 27 wherein Ar is 2-chloro-5-methoxyanilin-4-yl.

29. A pharmaceutical composition according to Claim 26 wherein Ar is group D, and p is 1.

30. A pharmaceutical composition according to Claim 29 wherein Ar is indol-3-yl.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01525

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D487/08; C07D471/08; A61K31/40
A61K31/435; A61K31/55; A61K31/53; A61K31/505

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,4 409 225 (BEECHAM) 11 October 1983 see column 1, line 54 - column 1, line 65; claim 1	1,25
P,A	EP,A,0 454 121 (SEARLE) 30 October 1991 (cited in the application) see page 26, line 41 - page 27, line 58; claim 1	1,25

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 JULY 1992	05.08.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201525 SA 58521

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/07/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4409225	11-10-83	None	
EP-A-0454121	30-10-91	AU-A- 7595191	07-11-91